

# **New Data on ARV Regimens for MTCT-Prevention**

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Tim Farley,<sup>a</sup> Dirk Buyse and Philippe Gaillard  
Department of Reproductive Health and Research  
World Health Organization, Geneva, Switzerland  
and Jos Perriens

and Department of Policy, Strategy and Research, UNAIDS, Geneva, Switzerland

At the 13<sup>th</sup> AIDS Conference in Durban new data from the following randomized clinical trials on the use of antiretrovirals (ARVs) to prevent mother to child transmission were presented:

- PETRA Trial (South Africa, Tanzania and Uganda)
- Perinatal HIV Prevention Trial (Thailand)
- ANRS/CDC pooled analysis - West Africa (Côte d'Ivoire and Burkina Faso)
- SAINT Study (South Africa)
- HIVNET012 trial (Uganda)
- BMS AI455-094 (South Africa).

Observational data from the USA addressed the efficacy and safety of combination ARVs.

The attached [tables](#) summarize these new results together with the previously available results.

### ***Short term efficacy (6 weeks to 3 months)***

A number of different antiretroviral (ARV) regimens have been shown to reduce the transmission of HIV from mother to child (Tables 1 and 2):

- Long course ACTG076/ANRS024 ZDV regimen starting from early pregnancy<sup>1</sup>
- Short course ARV regimens (ZDV, other ARV, combination of different ARVs), starting generally one month before delivery<sup>2-7</sup>
- Regimens starting in labour (combination ZDV+3TC or NVP regimens).<sup>8,9</sup>

Each regimen has advantages and disadvantages with respect to efficacy, potential toxicity, concerns for future treatment options, practicality and feasibility for implementation.

The early studies compared the efficacy of the ARV regimens against placebo (Table 1) and showed that short course regimens can reduce early transmission rates by 35% to 70% (that is, from about 25% to between 8% and 17%). The efficacy in breastfeeding populations<sup>3,4</sup> is lower than in populations where breastfeeding can be avoided.<sup>2</sup> The similarity of the results

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<sup>a</sup> Tel: +41 22 791 33 10, fax: +41 22 791 41 71, email: farleyt@who.int

from the two West African studies which both started ZDV from 36 weeks suggests that the addition of the 1 week post-partum dose for the mother in DITRAME did not confer any additional benefit. In the PETRA study<sup>10</sup> which compared combination ZDV + 3TC in three different regimens against placebo, Arm A (starting from 36 weeks) was more effective than Arm B (starting in labour), though not significantly so. Arm C (intrapartum only) showed no reduction in transmission rate compared with placebo.

More recent studies did not use a placebo control group, but studied the equivalence of different ARV regimens, most often including a short ZDV regimen (Table 2).

- The short-short arm of the PHPT study (from 35 weeks to 3 days postnatal) was significantly less effective than the long-long regimen (from 28 weeks to 6 weeks postnatal), and was dropped at the first interim analysis. At that time the transmission rates were 10.6% and 4.1%, respectively. The other three arms (long-short, short-long, long-long) showed comparable transmission rates (between 6% and 8%), except that the intrauterine transmission rate for the regimens starting at week 28 was 1.8%, significantly lower than the 5.0% observed with the short-long regimen starting from week 35. The authors concluded that while 6 weeks ZDV in infants may not add benefit when mothers had received the long antenatal treatment, it may prevent some infections when mothers receive only the shorter treatment.<sup>6</sup>
- The BMS A455-094 study presented preliminary results based on the first 204 women randomised. The preliminary results do not suggest any clear differences between the four regimens studied. The final study is anticipated to include a total of 360 women.<sup>7</sup>
- The HIVNET012 study showed that NVP was significantly more effective than an intrapartum-only ZDV regimen. This particular ZDV regimen has not been included in other studies. The study originally included a placebo arm that was dropped after results from the CDC Thailand study<sup>2</sup> became available. The transmission rate was 37% in women assigned placebo, compared with 20% among those concurrently assigned to the ZDV arm, based on 19 and 15 women respectively ( $P = 0.45$ ), suggesting that the ZDV regimen may have had some benefit.<sup>9</sup>
- The SAINT study, involving two regimens starting in labour, showed that the PETRA Arm B regimen (from onset of labour to 1 week postpartum and postnatal) was equivalent to a NVP regimen slightly different from that used in HIVNET012.<sup>8</sup>

An observational study from the USA in women receiving combination ARV treatments reported very low transmission rates – 1.1% among those receiving HAART and 3.9% among those receiving combination therapy which did not include a protease inhibitor.<sup>11</sup>

### ***Long-term efficacy (12 to 24 months)***

Three studies provided information on whether the short-term benefits of the different ARV regimens is maintained in infants exposed to HIV through breastfeeding (Table 3). The

pooled analysis from the West African studies showed that the difference in transmission rates at 3 months was still present up to 24 months.<sup>12</sup> Similarly for the HIVNET012 study up to 12 months follow-up.<sup>13</sup> By contrast the PETRA study reported that the differences seen in HIV-free survival between study arms at 6 weeks had decreased by 18 months.<sup>5</sup> However, it is unclear whether this diminution of the difference is due to increased HIV transmission or to non-HIV-related mortality. The PETRA Study team announced that further information on the exact timing of transmission through breastfeeding from their trial will be available in September 2000.

### ***ARV and transmission through breast feeding***

With all of the ARV regimens, transmission of HIV through breastfeeding remains a concern. The risk of HIV transmission through breastfeeding is in the range of 10 - 20% between birth and 18 to 24 months.<sup>14</sup> Factors associated with increased risk in transmission through breastfeeding include mother's viral load, low CD4 cell counts, clinically advanced HIV infection, and breast inflammatory or infectious processes. One study has suggested that exclusive breastfeeding is associated with a lower risk of HIV transmission than mixed feeding,<sup>15</sup> though this observation has yet to be confirmed by other research.

The investigators of both the PETRA and the CDC/ANRS study highlighted the importance of identifying interventions to prevent HIV transmission through breastfeeding. Work to address the issue of transmission through breast milk is already underway. Trials that assess the use of antiretrovirals to decrease breast milk transmission are being planned in a number of countries (Botswana, Côte d'Ivoire, Uganda and others). In addition methods to inactivate HIV in breast milk are being developed.<sup>16,17</sup>

### ***Drug resistance with Nevirapine***

WHO convened an expert panel in March 2000 to review the reported NVP resistance in mother infants pairs receiving NVP as part of an MTCT-prevention package.<sup>18</sup> The impact of these new data on the efficacy of the regimen in future pregnancies, future treatment options (of both mother and newborn), the disease progression and possibility of spread of resistant virus in the population was considered. The panel concluded that the new information was not considered sufficient to interfere with plans to make NVP more widely available in pilot MTCT-prevention programmes or in research settings. But there was insufficient information to recommend wide-scale implementation of NVP for MTCT prevention.<sup>19</sup>

At the Durban conference, the previous report from HIVNET006 of NVP-resistance observed in 20% of 15 women was confirmed in HIVNET012 where 7 of 30 transmitters showed selection of resistant virus at 6 weeks. In addition 3 of 7 infected infants showed resistance mutations.<sup>20</sup>

The changing time horizon for access to ARV treatment brings a new dimension to the question of drug resistance reported in women and children exposed to Nevirapine for MTCT prevention.

Where there is a reasonable expectation that non-nucleoside reverse transcriptase inhibitors (NNRTIs) will be used as part of treatment for HIV infection in either the mother or the child, considerations about resistance suggest that the use of an MTCT-prevention regimen which does not include NVP may be preferable. However, in settings where NNRTIs are not expected to be available in the near future, the costs and operational advantages of the NVP regimen make it a very attractive option. Such issues will be discussed at a consultation to be convened by WHO in October 2000 at which all information on the efficacy and safety of different ARV regimens, and the risks of transmission through breast milk will be reviewed.

## **Conclusion**

A range of ARV regimens are effective in reducing the MTCT of HIV. Each regimen has advantages and disadvantages with respect to efficacy, potential toxicity, concerns for future treatment options, and practicality and feasibility for implementation. Whatever ARV regimen is used, transmission of HIV through breastfeeding remains a concern.

These issues will be discussed in October 2000 at a consultation convened by WHO on behalf of the UNAIDS/UNFPA/UNICEF/WHO InterAgency Task Team on Mother to Child Transmission of HIV.

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